REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. By the present amendment, claims 1-6, 14-16, 19, and 20 are canceled. In addition, claims 7, 10, 17, and 21 are amended to independent format, and new claims 22-29 are added to more specifically recite certain aspects of the present invention. Support for these amendments is provided throughout the specification and claims as originally filed. Accordingly, these amendments do not constitute new matter.

Rejections under 35 U.S.C. § 102

Claims 1-6 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Young (U.S. Patent No. 5,023,087). More specifically, the Examiner asserts that Young discloses a liposomal formulation of liposomes containing an active agent and empty liposomes, wherein the ratio of liposomes containing active agent to empty liposomes is 0.1:1 to 10:200 and wherein the active agent is an anti-tumor agent. The Examiner further states that the liposomal formulation of Young is used to control the rate of release of the liposome-entrapped active agent.

Claims 1-6, 14-16, and 19-20 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 91/04019. Specifically, the Examiner alleges that this publication discloses a liposomal formulation of liposomes containing an active agent and empty lipsomes at a ratio of 1:1 to 1:10,000, wherein the liposomes comprise sphingomyelin and cholesterol within the claimed ratio, and the active agents include interferons and chemotactic peptides. In addition, the Examiner states that WO 91/04019 discloses that the addition of empty liposomes increases the bioavailability of the therapeutic agent.

Without acquiescence to these bases of rejection and solely to expedite prosecution of the instant application, Applicants have canceled claims 1-6, 14-16, and 19-20, thereby obviating these bases of rejection.

Rejections Under 35 U.S.C. § 103

Claims 7-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Young, the relevant teachings of which are described above. The Examiner concedes that Young does not teach the neoplastic agents recited in claims 7-16, but asserts that it would have been obvious to one of ordinary skill in the art to use the claimed neoplastic agents, based upon

Young's alleged teaching that the release rate of any active agent, irrespective of its nature, could be influenced by including empty liposomes.

Applicants respectfully traverse this basis of rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness in light of Young. To establish a *prima facie* case of obviousness, the following three criteria must be met: (1) the prior art must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; and (3) there must be a reasonable expectation of success. M.P.E.P., 8th Ed. § 2143. Applicants submit that Young fails to teach that the release rate of intravenously administered liposomal compositions can be influenced by including empty liposomes. Rather, the teachings of Young are strictly limited to intramuscularly and subcutaneously administered liposomal compositions. Therefore, since camptothecins and vinca alkaloids are known in the art to be administered intravenously, Young provides absolutely no motivation for the skilled artisan to include empty liposomes in liposomal formulations of these drugs and, therefore, fails to render the instant claims obvious.

As described in the instant specification, the presently claimed invention is based on Applicants' discovery that including empty liposomes in intravenously administered liposomal drug formulations increases the half-life of a drug in the bloodstream. In general, liposomes are cleared from the bloodstream by cells of the reticuloendothelial system (RES). Typically, the RES will remove 80-95% of a dose of injected liposomes within one hour, effectively out-competing a selected target site for uptake of the liposomes. Applicants discovered that by including empty liposome vesicles, it is possible to shield liposomes containing active agent from the RES. The empty liposome vesicles actually extend the blood circulation lifetime of the liposomes by acting as "decoys." In essence, the empty liposomal vesicles keep the RES busy and as a result, the serum half-life of the liposomes having active agent contained therein is increased.

Clearly, nothing taught or described in Young would bring the skilled artisan to this understanding or motivate the skilled artisan to add empty liposomes to liposomal drug formulations for intravenous administration. Indeed, Young states unequivocally that the field of

the invention is only relevant to intramuscular or subcutaneous delivery. *"The field of this invention, i.e., intramuscular or subcutaneous delivery of liposomal [sic] drug is not applicable and cannot be compared to the intravenous route of administration since the mechanism of drug release by the intramuscular route is entirely different, i.e. the liposomes are destabilized at the intramuscular or subcutaneous injection site thereby releasing the drug..."* (column 3, line 67 to column 4, line 6). Consistent with this disclosure, all claims in Young are directed to methods and compositions for SC or IM administration.

Further insight into why Young's teachings are only applicable to SC or IM administration is provided under the section titled "*B. Release Characteristics of Lipids and Encapsulated Compound*" (column 17, line 3 to column 18, line 42). For example, Young states that *"[t]he latter results indicate that lipid clearance is governed by bulk effects related to average liposome sizes, and forms the basis, according to one aspect of the invention, of controlling release characteristics of smaller liposomes by the addition of larger, empty ones*" (column 17, lines 52-57). And later, Young states *"[t]his finding suggests that liposomes are destabilized and release their encapsulated contents predominantly at the site of injection, with lipid clearance from the site being handled by a different, slower mechanism*" (column 17, line 68 to column 18, line 4). These statements indicate that bulk effects at the site of IM or SC injection influence the rate of destabilization of drug-loaded liposomes. Clearly, such bulk effects at a tissue site are not relevant for comparison to the fate of IV administered liposomes. In the case of IV administered liposomes, clearance from the plasma compartment predominantly reflects removal of drug-loaded liposomes by the RES. This mechanism is entirely distinct from those implicated by Young. Accordingly, the skilled artisan would have no expectation from the information provided in Young that the addition of empty liposomes to liposomal drug formulations would influence plasma pharmacokinetics following IV administration.

In light of these comments, Applicants submit that Young provides no motivation for the skilled artisan to include empty liposomes in liposomal drug formulations containing drugs that are administered intravenously, such as camptothecins and vinca alkaloids, as

presently claimed. Accordingly, Young fails to render the claimed invention obvious. Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Claims 7-13 and 19-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 91/04019, the relevant teachings of which are described above. The Examiner concedes that WO 91/04019 does not teach the neoplastic agents recited in claims 7-13 and 19-21, but asserts that it would have been obvious to one of ordinary skill in the art to use any active agent, since WO 91/04019 allegedly teaches that any active agent's bioavailability will be increased by including empty liposomes irrespective of its nature. Furthermore, the Examiner asserts that it would have been obvious to the skilled artisan to use sphingomyelin as suggested by WO 91/04019, and to vary the ratio of lipid to cholesterol to obtain the best possible results.

Applicants traverse this basis of rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness over WO 91/04019. Specifically, the teachings of WO 91/04019 would provide the skilled artisan no motivation to include empty liposome in liposomal formulations of drugs that are administered intravenously, such as the presently claimed camptothecins and vinca alkaloids, since, like Young, discussed above, WO 91/04019 is directed to methods and compositions for prolonging the bioavailability of therapeutic peptides or proteins after SC or IM administration.

While the constraint on the route of administration is not immediately obvious from the specification, upon careful review of the entirety of WO 91/04019, the skilled artisan would understand that its teachings are limited to SC and IM administration. For example, in the Summary of Invention, WO 91/04019 states, "*the liposome must be composed of suitable lipids such that it is relatively stable in lymph, but releases its contents readily in serum or plasma*" (page 4, lines 21-24). Further clarification is provided later in this section, wherein it states "*[t]he liposomes of the present invention are believed to prolong bioavailability by providing a vesicle which has sufficient structural integrity and characteristics which resist dissolution at the point of injection and in lymphatic system, while at the same time being amenable to gradual release of the encapsulated peptide or protein in the blood stream*" (page 4, line 32 to page 5, line 2). It is clear, therefore, from this disclosure that the bloodstream is not the site of injection,

and that the methods and compositions described in WO 91/04019 are intended for SC or IM administration. This is consistent with the Examples, which only describe SC administration.

Furthermore, WO 91/04019 shows that serum levels of hCT are increased when liposomal hCT is injected SC together with empty liposomes (Figure 1 and Figure 2). These data indicate that the extent of release of liposomal hCT, or released hCT, from the SC injection site to the plasma is increased when liposomal hCT is administered with empty liposomes. This is consistent with the disclosure in WO 91/04019 that the bioavailability of encapsulated peptides or proteins is increased when empty liposomes are added to the liposome-encapsulated agent (see for example page 5, line 34 to page 6, line 1). These data have no relevance to the present invention, which uses empty liposomes to reduce RES clearance of drug-loaded liposomes from the bloodstream.

As noted in discussion above of Young, and consistent with the teachings of Young, the SC or IM route of administration is not comparable to the IV route of administration. These differences are further exemplified by WO 91/04019. For example, WO 91/04019 states, "*the lipid vesicles containing the therapeutic peptide or protein are not so stable that they are taken up and consumed by macrophages prior to release of the therapeutic agent*" (page 5, lines 3-6). In contrast, according to the instant application, it is precisely because drug-loaded liposomes injected intravenously are taken up by macrophages that the addition of empty liposomes can increase their circulation lifetime in the blood. Clearly, therefore, WO 91/04019 provides no motivation for the skilled artisan to add empty liposomes to liposomal drug formulations for intravenous administration, and, thus, fails to render obvious the present invention, which is directed to including empty liposomes in liposomal drug formulations containing drugs that are understood by the skilled artisan to be administered intravenously, *i.e.*, camptothecins and vinca alkaloids. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kirpotin (U.S. Patent No. 6,110,491) in combination with either Young or WO 91/04019. Specifically, the Examiner asserts that Kirpotin discloses liposomal compositions, which may include sphingomyelin and cholesterol, wherein the active agent, which can be any compound

with ionizable groups, is in precipitated form. The Examiner concedes that Kirpotin fails to describe liposomal formulations that include empty liposomes, but asserts that it would have been obvious to one of ordinary skill in the art to further include empty liposomes, in light of Young's teachings that empty liposomes can be included to selectively control release rate or WO 91/04019's teachings that including empty liposomes increases the bioavailability of the encapsulated therapeutic agent.

Applicants respectfully traverse this basis of rejection and submit that the recited combination of references fails to render the claimed invention obvious, since the references fail to provide the requisite teaching or suggestion of the desirability of combining the teachings of the references to reach the present invention. Accordingly the present invention cannot be rendered obvious by a combination of these references.

Applicants submit that Kirpotin, as compared to Young and WO 91/04019, is directed to an entirely different area of liposome technology. Kirpotin describes an approach for achieving a high concentration of liposome-encapsulated drug, which involves encapsulating drug in a precipitated form. In stark contrast, Young and WO 91/04019 are generally directed to methods of controlling release or increasing bioavailability of SC or IM-administered liposome-encapsulated drugs by including empty liposomes. Indeed, the understanding in the art prior to the instant application was that increased levels of drug loading (such as described in Kirpotin) were associated with a higher rate of release. Therefore, a skilled artisan, in attempting to reduce the rate of release and increase bioavailability upon SC or IV administration, as described in Young or WO 91/04019, would not be motivated to utilize the methods of loading taught by Kirportin. Furthermore, none of these references provide any teaching or suggestion that these two methods could or should be combined to achieve the claimed invention drawn to liposomal formulations comprising both precipitated drug and empty liposomes. Certainly, Kirpotin certainly does not contemplate the use of empty liposomes, and Young and WO 91/04019 do not teach or contemplate the precipitation of drugs within liposomes. Accordingly, the skilled artisan would have no motivation to combine these references to achieve the claimed invention.

Applicants further submit that U.S. patent law clearly establishes that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having

ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992)). Since none of the cited references teach or suggest any advantage or desirability of modifying the teachings of the references to produce the claimed liposomal compositions comprising both precipitated drug and empty liposomes, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Claims 1-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with either Young or WO 91/04019. The Examiner submits that WO 99/13816 describes liposomal formulations containing various camptothecins in precipitated form, while conceding that it does not teach the use of empty liposomes. The Examiner alleges that the inclusion of empty liposomes in the compositions described in WO 99/13816 would be obvious to one of ordinary skill in the art, given Young's teachings that empty liposomes can be included to selectively control release rate or WO 91/04019's teachings that including empty liposomes increases the bioavailability of the encapsulated therapeutic agent.

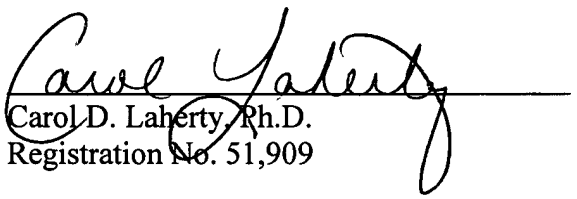
Applicants respectfully traverse this basis of rejection and submit that the recited combination of references fails to render the claimed invention obvious, essentially for the same reason that the previously cited combination of references fail to render the claimed invention obvious. Applicants submit that the references fail to provide the requisite teaching or suggestion of the desirability of combining the teachings of the references to reach the present invention. Accordingly the present invention cannot be rendered obvious by a combination of these references. Specifically regarding WO 99/13816, the teachings of this reference are limited to camptothecins, which are known in the art to be administered intravenously. Accordingly, the skilled artisan would have no motivation to modify the teachings of WO 99/13816 by adding empty liposomes to the liposomal camptothecin compositions described in WO 99/13816, on the basis of either Young or WO 91/04019, since their teachings regarding empty liposomes is clearly limited to SC and IM administered liposomal drug formulations, as described above, and as would be immediately appreciated by the skilled artisan. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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